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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/466,568	12/17/99	CRABTREE G	APV-316.16

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1636	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/466,568	CRABTREE ET AL.	
	Examiner	Art Unit	
	Bronwen M. Loeb	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 April 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6,14,17,18,20-24,30-33,36-39,45 and 48* is/are pending in the application.

4a) Of the above claim(s) *17,24,30,32,33 and 48* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6,14,17,18,20-24,30-33,36-39,45 and 48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

This action is in response to the Response to the Restriction Requirement, dated April 3, 2001. Claims 1, 6, 14, 17, 18, 20-24, 30-33, 36-39, 45 and 48 are pending.

Election/Restrictions

1. Applicant's election of Group I in Paper No. 11 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Group I includes claims 1, 6, 14, 18, 20-23, 31, 36-39 and 45. Claim 17 was erroneously listed in Group I in the Restriction Requirement mailed February 13, 2001, and therefore will not be examined in Group I. A phone message conveying this information was left on Beth Arnold's voice mail on April 23, 2001.

3. Claims 17, 24, 30, 32, 33 and 48 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions.

Priority

4. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. § 120 as follows:

> An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78).

Sequence Compliance

5. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 because sequences were set forth that lack sequence identifiers, no computer readable format (CRF) was filed, no paper sequence was filed and no attorney statement was filed. These sequences include **those in Figures 4A, B and C, and on page 21, line 31, page 27, line 18, page 42, line 14, page 49, lines 12, 14-15, and 26-27, page 57, line 31, page 58, lines 5-7, 13, 25, 26, and 34-36, page 59, lines 18 and 19, page 60, lines 3-5, 28, 29, and 34-36, page 61, lines 4-15 and page 76, lines 13-15**. If the Sequence Listing required for the instant application is identical to that of another application, a letter may be submitted requesting transfer of the previously filed sequence information to the instant application. For a sample letter requesting transfer of sequence information, refer to MPEP § 2422.05. Additionally, it is often convenient to identify sequences in figures by amending the Brief Description of the Drawings section (see MPEP § 2422.02).

Applicants are required to comply with all of the requirements of 37 CFR 1.821 through 1.825. Any response to this office action that fails to meet all of these requirements will be considered non-responsive. The nature of the noncompliance with the requirements of 37 C.F.R. 1.821 through 1.825 did not preclude the continued examination of the application on the merits, the results of which are communicated below.

Specification

6. The abstract of the disclosure is objected to because the abstract exceeds 150 words and contains more than one paragraph, as required by CFR 1.72(b). Correction is required.

7. The disclosure is objected to because of the following informalities: Figures 6, 13, 16, 18 and 23 have multiple panels, which is not reflected in the Brief Description of the

Figures. It would be remedial to amend the language to read, for instance, "Figs. 6A and B are..." on p. 10, line 33. The abbreviations used in Figure 15 are not defined: DAG, PKC, PLCγ1, $NFAT_C$ and $NFAT_N$. On p. 50, line 28, the cited figure should be Fig. 6A, not "Fig. 6". On p. 49, line 29, an unknown abbreviation "TAC" is recited. Pages 45, 47 and 57 contain what appear to be handwritten amendments to the specification.

Appropriate correction is required.

Claim Objections

8. Claim 18 is objected to because of the following informalities: the word "containing" is misspelled. Claim 21, lines 8-9 recite "and and". Appropriate correction is required.

Double Patenting

9. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10. Claims 18, 20 and 21 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-129 of U.S. Patent No. 6,165,787. Although the conflicting claims are not identical, they are not patentably distinct from each other because the issued claims drawn to cells comprising a genetic construct encoding a chimeric protein which comprises at least one ligand-binding domain and an action domain which induces a biological process when the ligand cross-links the chimeric proteins, are encompassed by and therefore anticipate the present claims.

11. Claims 18 and 20 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-76 of U.S. Patent No. 6,140,120. Although the conflicting claims are not identical, they are not patentably distinct from each other because the issued claims, drawn to a eukaryotic cell comprising a genetic construct encoding a chimeric protein comprising at least one ligand-binding domain which binds to a selected ligand to form a ligand-crosslinked protein complex and an intracellular targeting domain which causes cellular localization when crosslinked, are encompassed by and therefore anticipate the present claims.

12. Claim 31 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-21 of U.S. Patent No. 6,063,625. Although the conflicting claims are not identical, they are not patentably distinct from each other because the issued claims, drawn to a method for regulating expression of a target gene in a muscle cell comprising providing genetic constructs encoding a chimeric protein comprising a ligand binding domain and a transcriptional activation

domain, and a second chimeric protein encoding a ligand-binding domain and a DNA-binding domain wherein ligand binding forms a crosslinked complex and regulates transcription of a muscle cell gene under control of regulatory element to which the DNA-binding domain binds, is encompassed by and therefore anticipates the present claim.

13. Claims 1, 6 and 14 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-127 of U.S. Patent No. 6,046,047. Although the conflicting claims are not identical, they are not patentably distinct from each other because the issued claims, drawn to a genetic construct encoding a chimeric protein which comprises a ligand-binding domain and an intracellular targeting domain wherein formation of the ligand-crosslinked complex causes cellular localization, are encompassed by and therefore anticipate the present claims.

14. Claims 22 and 23 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 38 and 44 of U.S. Patent No. 6,043,082. Although the conflicting claims are not identical, they are not patentably distinct from each other because the issued claims, drawn to a DNA composition comprising two genetic constructs encoding first and second chimeric proteins, wherein the first protein comprises a ligand-binding domain which binds to a selected ligand to form a ligand-crosslinked protein complex and an action domain and the second protein comprises a ligand-binding domain and an intracellular targeting domain and further comprising a heterologous target gene under the expression control

of the ligand-crosslinked protein complex, are encompassed by and therefor anticipate the present claims.

15. Claim 31 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-70 of U.S. Patent No. 6,011,018. Although the conflicting claims are not identical, they are not patentably distinct from each other because the issued claims, drawn to a method for inducing expression of a target gene comprising providing a host animal containing a cell comprising a target gene and a genetic construct comprising a chimeric protein comprising a ligand-binding domain and an action, and administering to the animal the ligand which forms ligand-crosslinked complexes and which induce expression of the target gene, is encompassed by and therefore anticipates the present claim.

16. Claims 1, 6, 14, 18, 20 and 23 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-84, 86, 87, 106, 116 and 123-126 of U.S. Patent No. 5,869,337. Although the conflicting claims are not identical, they are not patentably distinct from each other because the issued claims drawn to a genetic construct encoding a chimeric protein comprising a ligand-binding domain and an action domain, a vector comprising the genetic construct, a cell comprising the construct, a DNA composition or a cell comprising the genetic construct and further comprising a genetic construct comprising a target gene under the control of the an oligomeric ligand-crosslinked protein complex, are encompassed by and therefore anticipate the present claims.

17. Claims 1, 6, 14, 18, 20, 21, 31 and 37-39 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-79, 81-93, 96-117, 161-218, 224-229 and 233-235 of U.S. Patent No. 5,834,266. Although the conflicting claims are not identical, they are not patentably distinct from each other because the issued claims, drawn to a genetic construct encoding a chimeric protein comprising a ligand-binding domain and an action domain that induces apoptosis following formation of the ligand-crosslinked complex, a vector comprising the genetic construct, a cell comprising the construct, a cell comprising the genetic construct and a second genetic construct encoding a second chimeric protein comprising a ligand binding domain and a transcriptional activating domain and further comprising a genetic construct comprising a target gene under the control of the an oligomeric ligand-crosslinked protein complex, a method for activating transcription of a gene comprising providing the aforementioned cell and administering ligand, and kits comprising the genetic construct, and further comprising a ligand, or a monomeric ligand which is an antagonist, is encompassed by and therefore anticipates the present claims.

18. Claim 31 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 3, 14, and 34-127 of U.S. Patent No. 5,830,462. Although the conflicting claims are not identical, they are not patentably distinct from each other because the issued claim, drawn to a method for inducing a biological process comprising providing a cell comprising at least one genetic construct comprising a ligand-binding domain and a DNA-binding domain and a second construct comprising a ligand-binding domain and a transcriptional activating domain, and a target

gene under the transcriptional control of a sequence to which the DNA-binding domain binds, and exposing the cell to ligand as as to induce ligand-crosslinked protein complex formation which then activates transcription of the target gene, is encompassed by and therefore anticipates the present claim.

19. Claim 18 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 44-54 of copending Application No. 09/582,916. Although the conflicting claims are not identical, they are not patentably distinct from each other because the pending claim, drawn to a genetically engineered primary mammalian cell containing a recombinant DNA construct encoding a fusion protein comprising a drug-binding domain wherein the drug is multivalent, and at least one signalling domain, is encompassed by and therefore anticipates the present claim.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

20. Claims 1, 6 and 18 are directed to an invention not patentably distinct from claims 4 and 10 of commonly assigned USP 6,117,680. Specifically, the issued claims, drawn to a recombinant nucleic acid encoding a fusion protein containing at least one domain derived from p65 transcription activation domain and a ligand-binding domain derived from FK506 binding protein, cyclophilin or FKBP:rapamycin complex binding domain, and a host cell containing the same, are encompassed by and therefore anticipate the present claims.

Commonly assigned USP 6,117,680, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 37 CFR 1.78(c) and 35 U.S.C. 132 to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g).

21. Claims 1, 6, and 18 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 4 and 10 of U.S. Patent No. 6,117,680. Although the conflicting claims are not identical, they are not patentably distinct from each other because , the issued claims, drawn to a recombinant nucleic acid encoding a fusion protein containing at least one domain derived from p65 transcription activation domain and a ligand-binding domain derived from FK506 binding protein, cyclophilin or FKBP:rapamycin complex binding domain, and a host cell containing the same, are encompassed by and therefore anticipate the present claims.

Claim Rejections - 35 USC § 101

22. Claim 45 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claim is drawn to "a host organism" which encompasses a human being, which is non-statutory subject matter.

23. Claim 45 is rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific asserted utility or a well-established utility.

The specification discusses the use of cells comprising a DNA construct encoding a chimeric protein for treatment of animals, especially mammals, which treatment would result in a host organism containing a cell comprising a DNA construct. This discussion is a credible, specific and substantial utility only for a cell comprising a DNA construct encoding a chimeric protein. However, there is no discussion of a utility for a host organism containing a cell that comprises a DNA construct encoding a chimeric protein.

24. Claim 45 is also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 112

25. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

26. Claim 36 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction of guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

The present claims are very broad. Claims 36 encompasses a method for providing a mammal responsive to a ligand comprising introducing at least one vector comprising a DNA construct encoding a chimeric protein and a selectable marker into a host mammal. The claim encompasses the delivery of a nucleic acid in vivo for therapeutic purposes which constitutes gene therapy and which is specifically contemplated in the specification.

The nature of the invention is a method for providing a mammal responsive to a ligand, wherein the ligand serves to oligomerize chimeric proteins encoded by at least one DNA construct and the oligomerization initiates a biological process, such a gene transcription, apoptosis, signal transduction, etc.

An analysis of the prior art as of the effective filing date of the present application shows the complete lack of documented success for any treatment based on gene

therapy. In a review on the current status of gene therapy, both Verma et al (Nature (1997) 389:239-242) and Palù et al (J. Biotechnol. (1999) 68: 1-13) state that despite hundreds of clinical trials underway, no successful outcome has been achieved. See Verma et al, p. 239, 1st paragraph; Palù et al, p. 1, Abstract. The on-going major obstacles to successful gene therapy are gene delivery and sustained expression of the gene. Regarding non-viral methods for gene delivery, Verma et al indicate that most approaches suffer from poor efficiency and transient expression of the gene (p. 239, col. 3, 2nd paragraph). Likewise, Luo et al (Nature Biotechnology (2000) 18:33-37) indicate that non-viral synthetic delivery systems are very inefficient. See p. 33, Abstract and col. 1, 1st and 2nd paragraphs. Regarding viral methods for gene delivery, both Verma et al and Palù et al teach the problem of adverse host immune responses to viral vectors. See Verma et al, p. 239, third column, second complete paragraph and Palù et al, p. 2, 2nd column, 1st full paragraph. While all three references indicate the promise of gene therapy, it is still a technique of the future and advancements in our understanding of the basics of gene delivery and expression must be made before gene therapy becomes a useful technique. See Verma et al, p. 242, col. 2-3; Palù et al, pp. 10-11; Luo et al, p. 33, col. 1, 1st paragraph.

The relative skill of those in the art of recombinant DNA techniques is high.

The area of the invention is unpredictable. As discussed above, the method of in vivo or ex vivo gene therapy is highly complex and unpredictable. Indeed, the recent tragic and unexpected death of a participant in a gene therapy clinical trial clearly illustrates the unpredictable nature of gene therapy. See Fox, ASM News, Feb. 2000,

66 (2): 1-3. The skilled artisan at the time the present invention was made recognized the difficulty of achieving sufficient heterologous gene expression to induce any therapeutic effect.

The present specification provides little or no guidance to support the claimed invention for gene therapy applications. The specification does not teach how many cells need to be transfected in an organism before the organism becomes responsive to the ligand. There are no teachings on how to achieve specificity in the transfection such that only the desired target cells are transfected. Furthermore, there is no direction provided as to how to overcome the obstacle to gene therapy recognized by leaders in the field, i.e. low efficiency of gene delivery and transient gene expression.

There are no working examples disclosed in which a host organism is made responsive to a ligand by transfecting the host organism.

The quantity of experimentation necessary to carry out the claimed invention is high, as the skilled artisan could not rely on the prior art or the present specification to teach how to use the claimed methods. In order to determine how to use the method to treat a condition, one of skill in the art would have to determine what effect exogenous transgene expression would have in any cell type, whether the effect could be exploited for treatment of a disease, how to deliver the given nucleic acid to the appropriate target cells with specificity and efficiency, and how to get sufficient expression to induce at least some therapeutic effect. Since neither the prior art nor the specification provides the answers to all of these questions, it would require a large quantity of trial and error experimentation by the skilled artisan to do so.

Based on the broad scope of the claims, the unpredictability in the area of the invention, the lack of sufficient guidance or working examples in the specification and the quantity of experimentation necessary, it would clearly require undue experimentation by one of skill in the art to determine how to use the method for providing a mammal responsive to a ligand.

27. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

28. Claims 1, 6, 14, 18, 20-23, 31, 36-39 and 45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 6, 18, 22, 23 and 31 recite the phrases "capable of binding", "capable of initiating", and/or "capable of expressing" which render the claims vague and indefinite. These phrases denote a latent ability, which may or may not be observed in the invention.

Claims 14, 18, 20, 21, 31 and 45 recite the word "containing" or "contains" which are vague and indefinite as they are not legally defined as open or closed words. It would be remedial to amend the claim language to recite "comprising" or "comprises" or "consisting of" or "consists of" as appropriate.

Claim 20 is vague and indefinite as it recites "a first DNA construct" but does not recite a second DNA construct.

Claim 21 is vague and indefinite because it recites "a first set of DNA constructs" in line 1 but not a second set of DNA constructs. Line 9 recites "a second DNA construct".

Claim 22 is vague and indefinite because it recites "a chimeric protein" in both steps (a) and (b). Does the second recitation refer to a second chimeric protein?

Claim 23 is vague and indefinite because it recites "a chimeric protein" in step (c). It is unclear if this is the chimeric protein of step (a), (b) or is a third chimeric protein.

Claim 31 recites the phrase "the oligomerization of said DNA construct" in step (a), which renders the claim vague and indefinite. The transcription control element is presumably responsive to the oligomerization *of the product* of the DNA construct, not to the oligomerization of the DNA construct itself.

Claim 31 recites the phrase "one DNA construct of claim 7" however claim 7 has been cancelled.

Claim 36 is vague and indefinite in reciting "a ligand of claim 14". Claim 14 is directed to a DNA vector, not a ligand. Claim 36 is also vague and indefinite as it lacks a step that clearly relates back to the preamble.

Claim Rejections - 35 USC § 102

29. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

30. Claims 1, 6, 18, 20, 22 and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Spencer et al (1993 Science 262: 1019-1024). Spencer et al teach chimeric protein constructs comprising FKBP12 and TCR γ chain. The product of the constructs binds to and can be oligomerized by FK1012 ligands. The TCR γ chain, when in oligomerized form, can activate an intracellular signal resulting in activating NF-AT, a transcription factor. The constructs are transfected into cells along with a reporter gene construct, plasmid NF-AT-SX then the cells are treated with ligand, which results in expression of the reporter gene. Monomeric ligand FK506 can act an antagonist to oligomerization by FK1012. See entire document.

31. Claims 1, 6, 14, 18, 20-23, 31, 37 and 38 are rejected under 35 U.S.C. 102(b) as being anticipated by Young et al (WO 95/34646). Young et al teach a first construct comprising a fusion protein comprising a peptide fused to a DNA binding domain and a second construct comprising a fusion protein comprising a peptide fused to a transcriptional activation domain. The two fusion proteins can be oligomerized by addition of a ligand which binds to the peptide domain of the fusion proteins. A reporter gene responsive to oligomer is also taught. The constructs are transfected into cells. Addition of the appropriate ligand results in expression of the reporter gene. See Fig. 3, p.4, line 25-p. 18, line 16 and Ex. 3 on p. 28-30.

32. Claims 1, 6, 14, 18, 20-23, 31, 36-39 and 45 are rejected under 35 U.S.C. 102(b) as being anticipated by Crabtree et al (USP 5,834,266). Crabtree et al teach a DNA construct encoding a chimeric protein comprising at least one receptor domain which binds a ligand fused to a heterologous protein domain which initiates a biological process upon exposure to a the ligand which oligomerizes the fusion proteins. The heterologous protein domain can be a protein which initiates a detectable intracellular signal, a DNA-binding domain, or a transcriptional activation domain. A DNA vector comprising the construct and a selectable marker is taught. A cell comprising at least one construct is taught. A cell comprising two different fusion protein constructs, wherein the heterologous protein domain is a DNA-binding domain in one construct and a transcriptional activation domain in the other construct, as well as a reporter gene is taught. A method of activating transcription using such cells is taught. Kits comprising at least one DNA construct, or further comprising either a ligand or a monomeric ligand are also taught. A host organism containing a cell that is transfected with at least one DNA construct is taught. See entire document.

33. Claims 1, 6, 14, 18, 20-23, 31, 37 and 38 are rejected under 35 U.S.C. 102(e) as being anticipated by Liu et al (USP 5,928,868). Liu et al teach a DNA construct encoding a chimeric protein comprising at least one receptor domain which binds a ligand fused to a heterologous protein domain which is a DNA-binding domain or a transcriptional activation domain; the fusion proteins are oligomerized by a ligand. A DNA vector comprising the construct and a selectable marker is taught. A cell comprising at least one construct is taught. A cell comprising two different fusion

protein constructs, wherein the heterologous protein domain is a DNA-binding domain in one construct and a transcriptional activation domain in the other construct, as well as a reporter gene is taught. A method of activating transcription using such cells is taught. Kits comprising at least one DNA construct, or further comprising a ligand is also taught. See Figs. 2, 3A-C and 6, col. 2, line 25-col. 9, line 21, and col. 13, line 59-col. 14, line 8.

34. Claims 1, 6, 14, 18, 20-23, 31 and 45 are rejected under 35 U.S.C. 102(b) as being anticipated by Rivera et al (Nature Medicine (1996) 2:1028-1032). Rivera et al teach a DNA construct encoding a chimeric protein comprising at least one receptor domain which binds a ligand fused to a heterologous protein domain which is a DNA-binding domain or a transcriptional activation domain; the fusion proteins are oligomerized by a ligand. A DNA vector comprising the construct and a selectable marker is taught. A cell comprising at least one construct is taught. A cell comprising two different fusion protein constructs, wherein the heterologous protein domain is a DNA-binding domain in one construct and a transcriptional activation domain in the other construct, as well as a reporter gene is taught. A method of activating transcription using such cells is taught. Kits comprising at least one DNA construct, or further comprising either a ligand or a monomeric ligand are also taught. A host organism containing a cell that is transfected with at least one DNA construct is taught. See entire document.

35. Claims 1, 6, 14 and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Arvidsson et al (Cell Growth and Differentiation 1992 3:881-887). Arvidsson et al teach genetic constructs comprising chimeric PDGF receptors, which comprise a ligand-

binding domain for PDGF and a signaling domain which induces mitogenicity in the cells. PDGF is a disulfide-bonded dimeric ligand which binds and dimerizes its receptor. The constructs were expressed in cells, from which it is inferred the construct was in a DNA vector with a selectable marker. See abstract.

36. Claims 20-23 and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Becker et al (Mol. Cell. Biol. 1989 9:3878-3887). . Becker et al teaches a cell (and a DNA composition) comprising a genetic construct encoding a chimeric protein comprising glucocorticoid receptor (GR) and the transcriptional activation domain of E1A. GR is a ligand-binding receptor which oligomerizes upon binding by ligand (such as dexamethasone) and then binds to DNA in a sequence-specific manner and activates transcription. The cell (and DNA composition) further comprises a CAT gene under the control of the viral early promoter (E3) to which E1A binds. A method for activating transcription is taught where the cell is provided with dexamethansome and expression of CAT is induced. See entire article.

37. Claims 1, 6, 18, 18, 20-23, and 31 are rejected under 35 U.S.C. 102(e) as being anticipated by Natesan et al (USP 6,117,680). Natesan et al teach a genetic construct encoding a chimeric protein comprising a ligand binding domain and a p65 tanscription activation domain. The ligand-binding domain may be FKBP and the synthetic divalent FKBP ligands are taught. Cells comprising the construct are taught. Also taught are a method for regulated gene expression comprising a construct encoding a DNA-binding domain fused to FKBP12 and a second construct encoding a transcription activation domain fused to the FRB domain of FRAP. In the presence of the ligand rapamycin,

the two fusion proteins oligomerize and induce expression of a gene under the regulatory control of the DNA-binding domain. See entire document.

Claim Rejections - 35 USC § 103

38. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

39. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

39. Claims 1, 6, 18, 20, 22, 31 and 37-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Spencer et al. Spencer et al do not teach a kit which comprises at least one DNA construct of a chimeric protein; or the kit which further comprising a ligand to which at least chimeric protein binds; or the kit which further comprises a monomeric ligand. A kit is a localized collection of materials, designed for

convenience. At the time the invention was made, it would have been obvious to one of ordinary skill in the art to assemble the materials needed for the method taught by Spencer et al into a localized collection. One would have been motivated to do so in order to work efficiently in the lab.

40. Claims 1, 6, 14, 18, 37 and 38 rejected under 35 U.S.C. 103(a) as being unpatentable over Arvidsson et al. Arvidsson et al do not teach a kit which comprises at least one DNA construct of a chimeric protein; or the kit which further comprising a ligand to which at least chimeric protein binds. A kit is a localized collection of materials, designed for convenience. At the time the invention was made, it would have been obvious to one of ordinary skill in the art to assemble the materials needed for the method taught by Spencer et al into a localized collection. One would have been motivated to do so in order to work efficiently in the lab.

It is noted that the rejections based on an incomplete priority claim may be overcome by perfecting the priority claim.

Conclusion

Claims 1, 6, 14, 18, 20-23, 31, 36-39 and 45 are rejected.

Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bronwen M. Loeb whose telephone number is (703) 605-1197. The examiner can normally be reached on Monday through Friday, from 10:00 AM to 6:30 PM. A phone message left at this number will be responded to as soon as possible (usually no later than the next business day after receipt by the examiner).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to Dianiece Jacobs, Patent Analyst whose telephone number is (703) 305-3388.

Bronwen M. Loeb, Ph.D.
Patent Examiner
Art Unit 1636

May 21, 2001

ROBERT A. SCHWARTZMAN
PRIMARY EXAMINER